UNITED STATES BANKRUPTCY COURT

SOUTHERN DISTRICT OF NEW YORK

PURDUE PHARMA L.P.,st al.	Chapter 11
Debtors,.	Case No. 19-23649 (RDD)
	Jointly administered

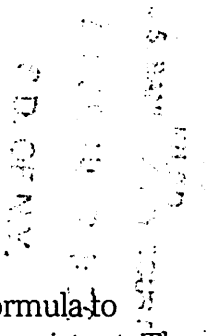
Plaintiffs' Motion for Summary Judgment

Plaintiffs move for summary judgment on all counts in their Verified Complaint

- Plaintiffs' Statement of Undisputed Facts,
- Exhibit 1, and Exhibit 2

Claimant Amanda Morales

Claim number 619945



Introduction

Purdue Pharma, the producer of **OxyContin**, stopped selling the original formula to pharmacies in August 2010 after reformulating the pills to make them crush-resistant. The reformulated pills make the drug more difficult to inject or snort, according to the FDA. This was 8 months after his death and the OxyContin he was prescribed was very strong containing a larger amount of oxycodone than after the reformation.

Centers for Disease Control and Prevention said that while deaths from drug overdoses had increased steadily in the decade ending in 2010, deaths attributable to opioid pain relievers increased fivefold for women between 1999 and 2010, and 3.6 times for men.In 2010, the CDC said, 16,651 died from overdoses involving opioids. That same year, the agency said enough opioid pain relievers were sold to medicate every adult in the United States with the typical dose of 5 milligrams of hydrocodone every four hours for a month — a 300 percent increase from barely a decade earlier.

Drugs may cause serotonin toxicity by a number of different mechanisms including inhibition of serotonin uptake and metabolism, increased serotonin synthesis and release, activation of serotonin receptors, and inhibition of cytochrome P450 oxidases. Some drug interactions involving opioids can increase intrasynaptic levels of serotonin, and opioid analgesic drugs are now recognized as being involved in some cases of serotonin toxicity especially if administered in conjunction with other serotonergic medications including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants.

Some drug interactions involving opioids can increase intrasynaptic levels of serotonin, and opioid analgesic drugs are now recognized as being involved in some cases of serotonin toxicity especially if administered in conjunction with other serotonergic medications including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants. In March 2016, the FDA issued a Drug Safety Communication concerning the association of the entire class of opioid pain medicines with serotonin toxicity. Reports of the involvement of individual opioids particularly tramadol, tapentadol, meperidine, methadone, oxycodone, fentanyl, and dextromethorphan are reviewed Serotonin syndrome remains an under recognized syndrome with the potential for life-threatening complications. In any patient taking a serotonergic agent, clinicians should look for subtle symptoms of serotonin syndrome including akathisia, agitation, tremor, anxiety, tachycardia, sweating, diarrhea, and mydriasis. The majority of physicians are unfamiliar with serotonin syndrome as a clinical diagnosis. Symptoms range from mild to life-threatening, with mild symptoms having the potential to be overlooked. The Toxicology Exposure Surveillance System reported toxic serotonin selective reuptake inhibitor exposures as 45,095 in 2010, with 97 of those cases having major adverse effects and six of those cases resulting in death.

Statement of facts

My father Ezzard Morales died on January 2, 2010 from an intoxication of oxycodone, amitriptyline, citrapram and tramadol. The combination of these medications caused serotonin syndrome and was fatal. My father was paranoid, restless, agitated and complained about being hot and sweating and complained about his muscles hurting. We suggested that he try to lay down and take a nap and try to relax. He was confused and his mental state was altered and he took more of his medication before laying down for his nap and was later found unconscious. My father was 37 years old when he died and I was only 16 years old at the time. I was close with my dad and was his only child. His birthday was on April 20 and mine is on April 21. My mom went into labor with me on his 21st birthday and he said I was the best birthday present he could have ever asked for. Losing my father left me without him in my life to love me, care for me, protect me, teach me and guide me as I was entering adulthood. I didn't have him to financially support me and the tragic loss I experienced made entering adulthood difficult and I struggled. His death could have been prevented if the warning label that took 6 years to warn people had been available for him to have cautioned him and his doctor about the dangers of serotonin syndrome. The cause of his death intoxication of oxycodone amitriptyline citrapram and tramadol are ALL on the list of medications that cause serotonin syndrome and are on the list of medications that the FDA safety announcement made on March 22, 2016. Not one but all 4 medications taken together were a very dangerous combination that purdue pharma didn't educate or inform doctors and the public about until years later and it was too late.

At the time of his death OxyContin didn't warn about the combination of medications that can cause serotonin syndrome. 6 years later the FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes. Safety Announcement[3-22-2016] The U.S. Food and Drug Administration (FDA) is warning

about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications. A search of the FDA Adverse Event Reporting System (FAERS) database for the period January 1, 1969, to June 12, 2013, identified 43 cases of serotonin syndrome in which opioids were used concomitantly with other serotonergic drugs. The review excluded meperidine, tramadol, and tapentadol, which were already labeled for the risk of serotonin syndrome at the time of the review. The most commonly reported opioids associated with serotonin syndrome were fentanyl (n=28), oxycodone (n=7), and methadone (n=5).

The diagnosis of serotonin syndrome depends on identifying autonomic instability, neuromuscular signs, and cognitive-behavioral changes in the presence of serotonergic medication use *(Table 3*[1,3,8,14]*)*.[1,14] Symptoms occur most commonly after serotonergic medications are added to therapeutic SSRI regimens, when dosages are changed, or after an overdose of serotonergic agents. Symptoms can develop rapidly, often within minutes of drug ingestion, although most patients present within six to 24 hours after a medication change or overdose.[1]

View/Print Table

Table 3.

Signs and Symptoms of Serotonin Syndrome

Agitation (restlessness)*
Diaphoresis*
Diarrhea*
Disseminated intravascular coagulation†
Fever above 100.4° F (38° C)
Hyperreflexia*
Incoordination (ataxia)*
Mental status changes

Confusion*

Hypomania*

Multi-organ failure†

Myoclonus*

Ocular clonus

Rhabdomyolysis†

Shivering*

Tonic-clonic seizures†

Tremor*

---

*—*Sternbach's diagnostic criteria require three of 10 signs and symptoms.*

†—*Extremely severe cases.*

Information from references 1, 3, 8, and 14.

The clinical manifestations of serotonin syndrome are highly variable. There are no specific laboratory tests to diagnose serotonin syndrome. The diagnosis should be based on the Hunter Serotonin Toxicity Criteria or Sternbach's criteria, although Hunter's criteria are more sensitive (84 versus 75 percent) and more specific (97 versus 96 percent) than Sternbach's.[14] Hunter's criteria use decision rules for predicting serotonin toxicity in patients who are known to have taken a serotonergic agent *(Figure 1)*.[14] Diagnosis with Hunter's criteria requires one of the following features or groups of features: spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia, temperature above 100.4°F (38°C), and ocular or inducible clonus. Sternbach's criteria require three of 10 clinical features coincident with an addition or recent increase of known serotonergic drugs to an established medication regimen.

The only thing that could have saved him would have been if there was adequate data, trials, education, warning and available knowledge for both patients and doctors at the time of his death. There wasn't enough information on any of these things until after he died and it was too late. I wish everyday that his death would have been avoided. There are no material facts that can be reasonably disputed that the cause of his death was a dangerous combination causing serotonin syndrome and failure to warn about these medications was an action skipped when ensuring that OxyContin was safely prescribed. There's nothing my father did to misuse or abuse his medications they were simply just a terrible combination causing serotonin syndromes. It's rare but it still happens and more education to the doctors to have prevented this would have made a difference. There needs to be appropriate accountability for the victims and their families who have lost loved ones due to Purdue Pharma fueling the opioid epidemic and pushing the sale of OxyContin.

My father died before the reformation of OxyContin later in 2010 and was given the OxyContin prior to the change to make it safer. He was given the OxyContin that was stronger and had greater risks associated with it.

Attached is a true and correct copy of Ezzard Morales autopsy report and the FDA safety announcement about the label changed. For the Court's convenience, the relevant portions of safety announcement and autopsy report have been highlighted. The Court already has his death certificate as proof of my claim.

Summary of argument

Failure to warn is one principle of product liability. When products **fail** to provide an adequate **warning** of the dangers associated with its use, this is known as **failure to warn**. The **warning** labels found on the product itself, and the owner's manual included with the product, must be clear and concise. Purdue Pharma failure to warn about the interactions with other medications that can cause a rare but fatal serotonin syndrome was reckless and negligent. Failure to have ensured physicians were properly educated and ensured that they had a clear understanding of risks and dangers wasn't done when Purdue Pharma wa pushing the sale of OxyContin in 2010. Proper education and awareness about serotonin syndrome will improve the accuracy of diagnosis and promote the institution of the appropriate treatment that may prevent significant morbidity and mortality.

It took six years after my father's death for there to be a warning label that clearly stated the list of medications that cause risks associated with serotonin syndrome. This could have been sooner and avoided a tragic loss for me and my family. The trials done before the warning label was changed should have been done before giving it to any patients and tests and reviews of trials like the one done prior to the label change in 2016 was done at an inappropriate time after thousands of people had been prescribed OxyContin and possibly risked serotonin syndrome and possibly death. The proper safety assessments and process that needed to be done was done in the wrong order and should have been done before prescribing OxyContin. More data and research needed to be readily available and

communicated with physicians and it could have saved my father's life. The dangers of serotonin syndrome were not clearly stated with the medications that interact with OxyContin and cause serotonin syndrome in 2009.

"In bankruptcy, summary judgment is governed in the first instance by Bankruptcy Rule 7056." In re Varrasso, 37 F.3d at 762. "By its express terms, the rule incorporates into bankruptcy practice the standards of Rule 56 of the Federal Rules of Civil Procedure." Id.; see also Fed. R. Bankr.P. 7056; Fed. R. Civ. P. 56(a) (which provides in pertinent part, that "[t]he court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law. The court shall state on the record the reason for granting or denying the motion.") "It is apodictic that summary judgment should be bestowed only when no genuine issue of material fact exists and the movant has successfully demonstrated an entitlement to judgment as a matter of law." In re Varrasso, 37 F.3d at 763 (citing Fed.R.Civ.P. 56(c)). "As to issues on which the nonmovant has the burden of proof, the movant need do no more than aver an absence of evidence to support the nonmoving party's case." Id. at 763, n. 1 (citation omitted). "The burden of production then shifts to the nonmovant, who, to avoid summary judgment, must establish the existence of at least one question of fact that is both genuine and material." Id. (internal quotations and citations omitted). The "mere existence of some alleged factual dispute between the parties will not defeat an otherwise properly supported motion for summary judgment; the requirement is that there be no genuine issue of material fact." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 247–48 (1986)(emphasis in the original).

Therefore, I Amanda Morales am entitled to summary judgment which should be granted. Wherefore, this Defendant requests that she be granted summary judgment as a matter of law. My situation with the serotonin syndrome that caused my father's death is different and I should not have to wait to have restitution and move on and get closure from this experience and do not want it going on longer than necessary. The points system which claimants will have their claim valued and based off of doesn't include fair considerations to my situation. I'm requesting summary judgment that will review my case and take into consideration how it's a rare and not under value the damage done to my life by having my dad die when I was still a teenager and needed him for so much. It could have been avoided and unfortunately my father nor his family were even aware or cautioned about the interactions with the combination of medications to have done anything to prevent it or request a different pain medication treatment for him, one that was safer. My claim should not have such little value when there was nothing my father did to have abused or misused his prescriptions. A fair carefully reviewed amount that takes into consideration the uniqueness of my case is all I'm seeking. Truthfully there's no amount that comes close to the dad I loved so dearly that I lost but the fact that the courts have offered some accountability for the lives lost and the families who have lost loved ones or struggle with addiction are great actions taken in the justice system. I understand that there's other claimants in this lawsuit and understand the urgency on both sides of the lawsuit to come to a resolution and so far there's been successful steps taken to get closer to the end goal which

is accountability, recognition of the problems, prevention for future problems and objectives for treatment for those who are in need of help with their addictions.

CERTIFICATE OF SERVICE

I hereby certify that a true and accurate copy of the foregoing document has been served upon :

United States Bankruptcy
Court Southern District of NY
Judge Robert D Drain

[Insert Attorney's Name/Address and Indicate Attorney for Appellant or Appellee]

by placing the same, postage prepaid in the United States Mail on this the 9th day of July, 2021.

Amanda Morales
[Signature]

Amanda Morales 205 Calle Del
Banco Bernalillo, NM 87004
[Party's address]

[Indicate here if acting *pro se*]

Exhibit 1

AUTOPSY REPORT
THE UNIVERSITY OF NEW MEXICO ◊ HEALTH SCIENCES CENTER
OFFICE OF THE MEDICAL INVESTIGATOR
School of Medicine Albuquerque, New Mexico 87131-5091

POSTMORTEM EXAMINATION

An autopsy is performed on the body of Ezzard Morales at the Office of the Medical Investigator, State of New Mexico, on the 3rd day of January 2010, starting at 10:45 AM.

The examination is performed under the legal authority of the Office of the Medical Investigator of the State of New Mexico.

The body is received within a sealed body bag, with a "State of New Mexico, Office of the Chief Medical Investigator" evidence label.

EXTERNAL EXAMINATION

The body is that of a well developed, obese, adult, White male who weighs 223 pounds, is 72 inches in length, and appears compatible with the stated age of 37 years. There are two OMI identification bands around the left wrist.

The body is received clad in blue athletic shorts only.

The body is cold. Rigor mortis is fully developed. Partially fixed red livor mortis extends over the posterior surfaces of the body, except in areas exposed to pressure.

The scalp hair is long and black. The irides are brown. The pupils are round. The corneae are clouded. The sclerae are white and the conjunctivae are clear. The nose and ears are normally formed. The decedent wears a trimmed black beard and mustache. The teeth are natural. The neck is unremarkable.

The thorax is well developed and symmetrical. The abdomen is obese and distended. The anus is free of lesions. The spine is normally formed and the surface of the back is free of lesions.

The external genitalia are those of a normal adult male.

The upper and lower extremities are well developed and symmetrical, without absence of digits.

Identifying marks and scars include a 6 x 4 inch faded tattoo on the upper back, an 8 inch x 1 inch tattoo of Gothic letters across the upper chest, 3 1/2 inch x 3/4 inch tattoo of the word "Amanda" on the left upper chest, a 4 x 4 inch tattoo on the right upper arm laterally, a 4 x 3 1/2 inch tattoo with the word "Morales" on the right forearm anteriorly, a 10 x 6 inch area of multiple tattoos on the left upper arm laterally, a 5 x 3 inch tattoo on the back of the left forearm, a tattoo of three dots on the back of the left hand on the webbing between thumb and index finger, a 3/4 inch x 1/2 inch faded tattoo on the back of the proximal phalanx of the left fourth finger.

There is no evidence of medical intervention.

EVIDENCE OF INJURY

HEAD AND NECK: Overlying the lateral aspect of the right eyebrow is a 3/4 inch laceration. There are no internal injuries.

INTERNAL EXAMINATION

BODY CAVITIES: No adhesions or abnormal collections of fluid are in any of the body cavities. All body organs are in normal and anatomic position.

HEAD (CENTRAL NERVOUS SYSTEM): The brain weighs 1440 grams. The dura mater and falx cerebri are intact, and not adherent to the brain. The leptomeninges are thin and transparent. There is no epidural, subdural or subarachnoid hemorrhage. The cerebral hemispheres are symmetrical. The structures at the base of the brain, including cranial nerves and blood vessels, are free of abnormality. Sections through the cerebral hemispheres reveal no lesions within the cortex, subcortical white matter, or deep parenchyma of either hemisphere. The cerebral ventricles are of normal caliber. Sections through the brain stem and cerebellum reveal no lesions.

NECK: Examination of the soft tissues of the neck, including strap muscles and large vessels, reveals no abnormalities. The hyoid bone and larynx are intact.

CARDIOVASCULAR SYSTEM: The heart weighs 450 grams. The pericardial sac is free of significant fluid or adhesions. The pericardial surfaces are smooth and glistening.

The coronary arteries arise normally and follow the distribution of a right dominant pattern and are involved with mild arteriosclerosis. None of the coronary arteries are compromised.

The chambers and valves are proportionate. The valves are normally formed, thin and pliable and free of vegetations.

The myocardium is dark red-brown, firm, and free of focal or regional fibrosis. The atrial and ventricular septa are intact.

The aorta and its major branches arise normally and follow the usual course, with no significant atherosclerosis. The orifices of the major aortic vascular branches are patent. The vena cava and its major tributaries are patent and return to the heart in the usual distribution.

RESPIRATORY SYSTEM: The right and left lungs weigh 830 and 770 grams, respectively. The upper and lower airways contain a small amount of

aspirated gastric contents. The mucosal surfaces are smooth and purple-tan. The pleural surfaces are smooth and glistening. The pulmonary parenchyma is dark red-purple and the cut surfaces exude marked amounts of bloody fluid. The pulmonary arteries are normally developed and without thromboemboli.

LIVER AND BILIARY SYSTEM: The liver weighs 2230 grams. The hepatic capsule is smooth, glistening, and intact, covering yellow-brown parenchyma. The gallbladder contains viscid bile. The extrahepatic biliary tree is patent.

ALIMENTARY TRACT: The esophagus is lined by gray-white smooth mucosa. The gastric mucosa is autolyzed and the lumen contains 800 ml. of partially digested food particles. The serosa of the small bowel is smooth and glistening. The small bowel contains partially digested food. There are no mucosal lesions of the small bowel. The colon contains unformed stool. In the cecum, there are focal serpiginous areas of pseudomembranous colitis. The appendix is present. The pancreas has a soft purple-tan lobulated appearance.

GENITOURINARY TRACT: The right and left kidneys weigh 180 and 160 grams, respectively. The renal capsules are smooth, thin, semitransparent, and strip with ease from the underlying smooth, red-brown, firm, cortical surfaces. The cortices are of normal thickness and delineated from the medullary pyramids. The calyces, pelves, and ureters are non-dilated and free of stones. The urinary bladder contains 45 ml. of yellow urine; the mucosa is gray-tan and smooth.

The bilaterally descended testes are small but have a normal consistency. The prostate is not enlarged.

RETICULOENDOTHELIAL SYSTEM: The spleen weighs 390 grams and has a smooth intact capsule covering red-purple moderately firm parenchyma. The splenic white pulp is grossly indiscernible.

ENDOCRINE SYSTEM: The pituitary gland is of normal size. The thyroid gland is of normal position, size and texture. The adrenal glands have normal cut surfaces with yellow cortex and gray medulla.

MUSCULOSKELETAL SYSTEM: The bony framework, supporting musculature, and soft tissues are not unusual. The cervical spinal column is stable on internal palpation.

MICROSCOPIC EXAMINATION

Microscopic slide key

A1: Heart
A2: Lungs
A3: Kidney; Liver

A4: Colon

Heart: negative
Lungs: anthracosis; autolysis; edema
Kidney: autolysis
Liver: mild fatty change; chronic non-specific hepatitis
Colon: ischemic changes with bowel wall necrosis and acute inflammation; mucosal hemorrhage

PATHOLOGIC DIAGNOSES

I. Acute intoxication by combined action of oxycodone, amitriptyline, citalopram, and tramadol
   A. Pulmonary congestion and edema
   B. Agonal aspiration of gastric contents
   C. Ischemic hemorrhagic colitis
II. Mild coronary arteriosclerosis
III. Fatty change of liver
IV. Chronic non-specific hepatitis
V. Colonic diverticulosis
VI. Laceration of face

OPINION

This 37-year-old male, Ezzard Morales, died as a result of an overdose of his prescription medications.

According to reports, he appeared intoxicated and seemed paranoid. He was put in bed but later found unresponsive. He had a history of previous alcohol abuse and cocaine abuse. He was also prescribed OxyContin, Amitriptyline and Gabapentin, and the prescriptions were not within normal limits.

At autopsy, there was evidence of a laceration overlying the right eyebrow, consistent with a terminal collapse. There were no internal injuries and no significant natural disease to explain the death. There was fatty change of the liver consistent with chronic alcoholism.

Toxicologic evaluation revealed high concentrations of oxycodone (Oxycontin), amitriptyline (Elavil), citalopram (Celexa), and tramadol (Ultram).

The manner of death is accident.

Ross E. Zumwalt M.D.

AUTOPSY REPORT
THE UNIVERSITY OF NEW MEXICO ◊ HEALTH SCIENCES CENTER
OFFICE OF THE MEDICAL INVESTIGATOR
School of Medicine Albuquerque, New Mexico 87131-5091

Chief Medical Investigator

All Signatures Electronically Authenticated

Final Date: 01/16/2010

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Robert A. Middleberg, PhD, DABFT, DABCC-TC, Laboratory Director

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Toxicology Report

Report Issued 01/14/2010 10:00

To: **20141**
New Mexico Office of Medical Investigators
Attn: Amy Boule
MSC11 6030 1 UNM
Albuquerque, NM 871310001

Patient Name	MORALES, EZZARD
Patient ID	2010-01029
Chain	11111811
Age	37 Y
Gender	Male
Workorder	10003251

Positive Findings:

Compound	Result	Units	Matrix Source
Caffeine	Positive	mcg/mL	Heart Blood
Cotinine	Positive	ng/mL	Heart Blood
Ibuprofen	Positive	mcg/mL	Heart Blood
Nicotine	Positive	ng/mL	Heart Blood
Theobromine	Positive	mcg/mL	Heart Blood
Oxycodone - Free	260	ng/mL	Heart Blood
Amitriptyline	460	ng/mL	Heart Blood
Nortriptyline	1200	ng/mL	Heart Blood
Trazodone	0.17	mcg/mL	Heart Blood
Meprobamate	1.0	mcg/mL	Heart Blood
Citalopram / Escitalopram	810	ng/mL	Heart Blood
Tramadol	240	ng/mL	Heart Blood
O-Desmethyltramadol	73	ng/mL	Heart Blood
Opiates	Presump Pos	ng/mL	Urine

See Detailed Findings section for additional information

Testing Requested:

Analysis Code	Description
8050U	Postmortem Toxicology - Urine Screen Add-on (6-MAM Quantification only)
8052B	Postmortem Toxicology - Expanded, Blood

Specimens Received:

ID	Tube/Container	Volume/ Mass	Collection Date/Time	Matrix Source	Miscellaneous Information
001	Gray Top Tube	10.25 mL	01/03/2010	Heart Blood	
002	White Plastic Container	16 mL	01/03/2010	Urine	

All sample volumes/weights are approximations.

Specimens received on 01/07/2010.

NMS

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Workorder 10003251
Chain 11111811
Patient ID 2010-01029

Detailed Findings:

Analysis and Comments	Result	Units	Rpt. Limit	Specimen Source	Analysis By
Caffeine	Positive	mcg/mL	0.10	001 - Heart Blood	GC/MS
Cotinine	Positive	ng/mL	12	001 - Heart Blood	GC/MS
Ibuprofen	Positive	mcg/mL	10	001 - Heart Blood	GC/MS
Nicotine	Positive	ng/mL	12	001 - Heart Blood	GC/MS
Theobromine	Positive	mcg/mL	5.0	001 - Heart Blood	GC/MS
Oxycodone - Free	260	ng/mL	10	001 - Heart Blood	GC/MS
Amitriptyline	460	ng/mL	10	001 - Heart Blood	GC
Nortriptyline	1200	ng/mL	10	001 - Heart Blood	GC
Trazodone	0.17	mcg/mL	0.10	001 - Heart Blood	GC
Meprobamate	1.0	mcg/mL	1.0	001 - Heart Blood	GC
Citalopram / Escitalopram	810	ng/mL	5.0	001 - Heart Blood	GC
Tramadol	240	ng/mL	20	001 - Heart Blood	LC-MS/MS
O-Desmethyltramadol	73	ng/mL	20	001 - Heart Blood	LC-MS/MS
Opiates	Presump Pos	ng/mL	300	002 - Urine	EIA

Based on this screening result, confirmation testing was performed. Refer to the confirmation test result(s).

Other than the above findings, examination of the specimen(s) submitted did not reveal any positive findings of toxicological significance by procedures outlined in the accompanying Analysis Summary.

Reference Comments:

1. Amitriptyline (Elavil®, Endep®) - Heart Blood:

   Amitriptyline is a tricyclic compound used in the treatment of depression. The compound undergoes extensive metabolism, and its major metabolite, nortriptyline, is also active as an antidepressant.

   Optimal patient response is usually observed when plasma concentrations of amitriptyline plus nortriptyline range from 80 - 200 ng/mL.

   A reported range of amitriptyline blood concentrations in fatalities from ingestion of amitriptyline range from 3000 - 15000 ng/mL.

   Post-mortem blood concentrations of tricyclic antidepressants and structurally-related compounds may depend on the anatomic source of the blood specimen. Concentrations may be higher in blood from visceral organs and the major vessels associated with them than actual ante-mortem circulating levels.

2. Caffeine (No-Doz) - Heart Blood:

   Caffeine is a xanthine-derived central nervous system stimulant. It also produces diuresis and cardiac and respiratory stimulation. It can be readily found in such items as coffee, tea, soft drinks and chocolate. As a reference, a typical cup of coffee or tea contains between 40 to 100 mg caffeine.

   Following the oral ingestion of 120 and 300 mg of caffeine, reported peak plasma concentrations of the drug averaged 3.0 mcg/mL (range, 2.0 - 4.0 mcg/mL) and 7.9 mcg/mL (range, 6.0 - 9.0 mcg/mL), respectively. A single oral dose of 500 mg produced a reported peak plasma concentration of 14 mcg/mL after 30 min.

   Reported concentrations of caffeine in caffeine-related fatalities averaged 183 mcg/mL (range, 79 - 344 mcg/mL).

   The reported qualitative result for this substance is indicative of a finding commonly seen following typical use and is usually not toxicologically significant.

NMS

CONFIDENTIAL

Workorder 10003251
Chain 11111811
Patient ID 2010-01029

Reference Comments:

3. Citalopram / Escitalopram (Celexa®, Lexapro®) - Heart Blood:

   Citalopram (Celexa®) is a selective serotonin reuptake inhibitor (SSRI) that increases brain levels of serotonin, a chemical that is thought to be linked to mood, emotions, and mental state. The drug is indicated for use as an antidepressant. Citalopram is a racemic mixture of S- and R-enantiomers and the S-enantiomer is more potent than the R-enantiomer. Steady-state serum or plasma levels from patients on a daily regimen of 30 to 60 mg of citalopram range from 9 - 200 ng/mL.

   Adverse effects due to acute overdosage with 600 mg or more of citalopram may include EKG abnormalities and seizures. In postmortem blood, concentrations in documented fatalities involving citalopram have ranged from 3400 - 11000 ng/mL.

   Escitalopram (Lexapro®) is the S-enantiomer of racemic citalopram and it also is indicated for use in the treatment of depression. It binds with greater affinity to the serotonergic transporter than the R-enantiomer. Steady-state peak plasma levels from patients on regimen of 10 or 30 mg/day of escitalopram were reported as 21 and 64 ng/mL, respectively, and occur at approximately 4 hours post dose.

   This test is not chiral specific; therefore, citalopram and/or escitalopram may be present.

4. Cotinine (Nicotine Metabolite) - Heart Blood:

   Cotinine is a metabolite of nicotine and may be encountered in the fluids and tissues of an individual as a result of, e.g., tobacco exposure. Concentrations may be variable in blood and urine depending on the route of exposure and length of exposure. Cotinine plasma/serum concentrations in non-smokers are reported to be typically less than 15 ng/mL. Tobacco users and transdermal patch wearers have typical cotinine plasma/serum concentrations of less than 1000 ng/mL.

   Anabasine is a natural product occurring in tobacco, but not in pharmaceutical nicotine and a separate test for anabasine in urine can be used to distinguish tobacco from pharmaceutical nicotine use.

5. Ibuprofen (Motrin®) - Heart Blood:

   Ibuprofen is a non-narcotic analgesic and anti-inflammatory agent available in prescription and non-prescription dosages. Daily oral doses generally range from 900 to 2400 mg.

   Following a single 400 mg oral dose, an average peak plasma concentration of 28 mcg/mL (range, 17 to 36 mcg/mL) was reported. No accumulation of ibuprofen in plasma was reported after 200 mg t.i.d. for 2 weeks.

   In overdose, ibuprofen produces effects such as nausea, vomiting, diarrhea, vision disturbances, edema and dizziness. In a reported overdose, the postmortem blood level was 81 mcg/mL.

   The reported qualitative result for this substance is indicative of a finding commonly seen following typical use and is usually not toxicologically significant.

6. Meprobamate (Carisoprodol Metabolite) - Heart Blood:

   Meprobamate is a DEA Schedule IV sedative, antianxiety and muscle relaxant agent. The normal therapeutic adult dosage ranges from 200 to 800 mg and should not exceed 2400 mg daily. This compound is also the active metabolite of the skeletal muscle relaxant carisoprodol (Soma®).

   Following a single oral 400 mg dose, average plasma meprobamate concentrations of 7.7 mcg/mL at 2 hr, 4.4 mcg/mL at 8 hr and 1.6 mcg/mL at 24 hr. were reported. After ingestion of a 1600 mg dose, an average blood concentration of meprobamate of 24 mcg/mL was reported over a 1.5 hr. period.

   Meprobamate produces central nervous system depression similar to barbiturates and has physical dependence addiction liability equal to that of barbiturates. Meprobamate is capable of producing an outward appearance of intoxication and derangement and impairment of alertness, judgment, sense of care and caution and nerve-muscle coordination. Sudden withdrawal of this drug can result in seizures and death.

   Overdose with meprobamate results in stupor, coma, hypotension and respiratory depression with blood concentrations generally exceeding 50 mcg/mL. In fatal overdose cases, blood concentrations have been reported to range from 35 - 410 mcg/mL.

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Workorder	10003251
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Patient ID	2010-01029

Reference Comments:

7. Nicotine - Heart Blood:

   Nicotine is a potent alkaloid found in tobacco leaves at about 2 - 8% by weight. It is also reportedly found in various fruits, vegetables and tubers, e.g., tomatoes and potatoes, but at a smaller per weight fraction. As a natural constituent of tobacco, nicotine is found in all commonly used smoking or chewing tobacco products. It is also in smoking cessation products, e.g., patches. Nicotine has been used as a pesticide, although not as widely since the advent of more effective agents.

   Nicotine is extensively metabolized; the primary reported metabolite is the oxidative product cotinine. The plasma half-life of nicotine is short (approximately 1 - 2 hr); while that of cotinine is about 20 hr. Non-smokers typically have plasma/serum nicotine concentrations of less than 10 ng/mL; however, levels may be higher depending on exposure parameters, e.g., length of time in a tobacco smoke environment; amount of airborne nicotine, etc. Tobacco users and transdermal patch wearers have typical nicotine plasma/serum concentrations less than 100 ng/mL. However, many factors influence the levels found in an individual, including: frequency of use; amount of nicotine exposed to; route of administration; etc.

   Toxic effects of nicotine overdose include nausea, vomiting, dizziness, sweating, miosis, EEG and ECG changes, tachycardia, hypertension, respiratory failure, seizures and death. Death from nicotine exposure usually results from either a block of neuromuscular transmission in respiratory muscles or from seizures. Reported blood levels of nicotine in deaths attributed to the compound range from 1000 - 5800000 ng/ml .

   Anabasine is a natural product occurring in tobacco, but not in pharmaceutical nicotine. A separate test for anabasine in urine can be used to distinguish tobacco from pharmaceutical nicotine use.

   The reported qualitative result for nicotine is indicative of a finding commonly seen following typical use and is usually not toxicologically significant.

8. Nortriptyline (Amitriptyline Metabolite, Aventyl®, Pamelor®) - Heart Blood:

   Nortriptyline is a tricyclic antidepressant drug used in the treatment of affective (mood) disorders, principally major depression. It is also a metabolite of the antidepressant amitriptyline (Elavil®).

   Peak plasma levels are achieved at about 8 hr. Optimal therapeutic plasma levels for control of depression range from 50 - 150 ng/mL. Following chronic daily oral doses of 150 - 250 mg, reported steady-state plasma levels averaged 170 - 380 ng/mL, respectively.

   At plasma levels exceeding 200 ng/mL, toxic side effects such as hyper- or hypotension, tachycardia, cardiac arrhythmias, confusion and nausea may be present; severe overdose may result in convulsions, coma and cardiac irregularities. Following ingestion of 2000 mg of nortriptyline, a plasma concentration of 900 ng/mL was reported in a patient who later died after ventricular tachycardia, convulsions and then cardiovascular collapse.

   Postmortem blood concentrations of tricyclic antidepressants can depend on the anatomic source of the blood specimen. Concentrations may be higher in blood from visceral organs and the major vessels associated with them than actual antemortem circulating levels.

9. O-Desmethyltramadol (Tramadol Metabolite) - Heart Blood:

   Peak plasma concentration for O-Desmethyltramadol following a single 100 mg oral dose: 35 - 75 ng/mL. Steady-state plasma concentration following a 100 mg 4 times daily regimen: 80 - 140 ng/mL.

10. Oxycodone - Free (OxyContin®, Roxicodone®) - Heart Blood:

    Oxycodone is a DEA Schedule II controlled semi-synthetic narcotic analgesic. It is used to control pain associated with such ailments as bursitis, injuries, simple fractures and neuralgia. The addiction liability of oxycodone is about the same as for morphine. This compound should be administered in the smallest effective dose and as infrequently as possible. The usual adult dose of the hydrochloride salt is 5 mg every 6 hr.

    Following the oral administration of oxycodone as both sustained-release (Oxycontin®) and regular formulations, peak plasma concentrations of the compound are generally less than 100 ng/mL; however, the sustained-release preparation may also result in peak concentrations of oxycodone less than 10 ng/mL serum.

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Reference Comments:

Oxymorphone is a pharmacologically active metabolite of oxycodone that may be seen in blood in very low concentrations.

In overdose, oxycodone can produce stupor, coma, muscle flaccidity, severe respiratory depression, hypotension and cardiac arrest. In two oxycodone-related suicides, blood concentrations of 4300 and 14000 ng/mL were reported. However, sustained-release preparations appear to produce adverse reactions, up to and including death, at concentrations of oxycodone well less than 1000 ng/mL, especially in combination with other central nervous system depressants, depending on use pattern and route of administration.

11. Theobromine (Xantheose) - Heart Blood:

Theobromine is a methylxanthine alkaloid found in tea and cocoa products and has been reported to pass into the breast milk of nursing mothers. Theobromine has the general properties of the xanthines, including diuresis and smooth muscle stimulation.

12. Tramadol (Ultram®, Ultrex®) - Heart Blood:

Tramadol is a synthetic opioid receptor agonist used for the management of moderate to moderately severe pain. Peak plasma levels of tramadol following a single 100 mg oral dose range from 230 - 380 ng/mL and peak levels of the active metabolite, O-desmethyltramadol, range from 35 - 75 ng/mL. Steady-state plasma levels following an oral dosage regimen of 100 mg of tramadol administered 4 times a day range from 420 - 770 ng/mL. The elimination half-lives of tramadol and O-desmethyltramadol are 5 to 8 hours and 6 to 9 hours, respectively.

Common adverse reactions to tramadol include sedation, dizziness, headache, and constipation. Higher doses may elicit agitation, tachycardia, hypertension and seizures. The mean postmortem femoral blood concentration of tramadol in 5 individuals who died due to tramadol overdose was reported as 6100 ng/mL.

13. Trazodone (Desyrel®) - Heart Blood:

Trazodone is a structurally atypical antidepressant agent. It is prescribed for the treatment of major depression. There is a wide range of trazodone dose requirements; however, total daily oral dosages should not exceed 400 mg for outpatients and 600 mg for hospitalized patients.

The expected steady-state therapeutic range for trazodone is 0.5 - 1.2 mcg/mL. In older patients the range may be extended to 5.0 mcg/mL.

The principal effects of trazodone overdosage include drowsiness and lethargy. The CNS-depressant effects of trazodone are at least additive with other CNS-depressants, e.g., barbiturates, benzodiazepines and alcohol. Two reported fatalities related to trazodone overdose had blood concentrations of the drug at 15 and 23 mcg/mL.

Sample Comments:

001 Physician/Pathologist Name: ZUMWALT

Chain of custody documentation has been maintained for the analyses performed by NMS Labs.

Unless alternate arrangements are made by you, the remainder of the submitted specimens will be discarded six (6) weeks from the date of this report; and generated data will be discarded five (5) years from the date the analyses were performed.

Workorder 10003251 was electronically signed on 01/14/2010 09:36 by:

Susan B. Crookham

Susan Crookham,
Certifying Scientist

Analysis Summary and Reporting Limits:

Acode 50013B - Cannabinoids Confirmation, Blood (Forensic) - Heart Blood

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Workorder 10003251
Chain 11111811
Patient ID 2010-01029

Analysis Summary and Reporting Limits:

-Analysis by Gas Chromatography/Mass Spectrometry (GC/MS) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
11-Hydroxy Delta-9 THC	5.0 ng/mL	Delta-9 THC	1.0 ng/mL
Delta-9 Carboxy THC	5.0 ng/mL		

Acode 50016B - Opiates - Free (Unconjugated) Confirmation, Blood (Forensic) - Heart Blood

-Analysis by Gas Chromatography/Mass Spectrometry (GC/MS) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
6-Monoacetylmorphine - Free	10 ng/mL	Hydromorphone - Free	10 ng/mL
Codeine - Free	10 ng/mL	Morphine - Free	20 ng/mL
Dihydrocodeine / Hydrocodol - Free	10 ng/mL	Oxycodone - Free	10 ng/mL
Hydrocodone - Free	10 ng/mL	Oxymorphone - Free	10 ng/mL

Acode 50019U - Heroin Metabolite Confirmation - Free (Unconjugated), Urine (Forensic)

-Analysis by Gas Chromatography/Mass Spectrometry (GC/MS) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
6-Monoacetylmorphine - Free	10 ng/mL		

Acode 52004B - Antidepressants Confirmation, Blood (Forensic) - Heart Blood

-Analysis by Gas Chromatography (GC) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Amitriptyline	10 ng/mL	Imipramine	10 ng/mL
Amoxapine	0.010 mcg/mL	Maprotiline	10 ng/mL
Clomipramine	10 ng/mL	Mirtazapine	5.0 ng/mL
Desipramine	10 ng/mL	Norfluoxetine	10 ng/mL
Desmethylclomipramine	10 ng/mL	Nortriptyline	10 ng/mL
Desmethyldoxepin	10 ng/mL	Protriptyline	10 ng/mL
Desmethyltrimipramine	10 ng/mL	Tranylcypromine	10 ng/mL
Doxepin	10 ng/mL	Trazodone	0.10 mcg/mL
Fluoxetine	10 ng/mL	Trimipramine	10 ng/mL

Acode 52017B - Carisoprodol and Metabolite Confirmation, Blood (Forensic) - Heart Blood

-Analysis by Gas Chromatography (GC) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Carisoprodol	0.20 mcg/mL	Meprobamate	1.0 mcg/mL

Acode 52021B - Citalopram Confirmation, Blood (Forensic) - Heart Blood

-Analysis by Gas Chromatography (GC) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Citalopram / Escitalopram	5.0 ng/mL		

Acode 52128B - Tramadol and Metabolite Confirmation, Blood (Forensic) - Heart Blood

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Workorder 10003251
Chain 11111811
Patient ID 2010-01029

Analysis Summary and Reporting Limits:

-Analysis by High Performance Liquid Chromatography/Tandem Mass Spectrometry (LC-MS/MS) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
O-Desmethyltramadol	20 ng/mL	Tramadol	20 ng/mL

Acode 8050U - Postmortem Toxicology - Urine Screen Add-on (6-MAM Quantification only)

-Analysis by Enzyme Immunoassay (EIA) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Amphetamines	1000 ng/mL	Methadone	300 ng/mL
Barbiturates	0.30 mcg/mL	Opiates	300 ng/mL
Benzodiazepines	50 ng/mL	Phencyclidine	25 ng/mL
Cannabinoids	20 ng/mL	Propoxyphene	300 ng/mL
Cocaine / Metabolites	300 ng/mL		

Acode 8052B - Postmortem Toxicology - Expanded, Blood - Heart Blood

-Analysis by Colorimetry (C) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Acetaminophen	5.0 mcg/mL		

-Analysis by Colorimetry (C) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Salicylates	200 mcg/mL		

-Analysis by Enzyme-Linked Immunosorbent Assay (ELISA) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Barbiturates	0.040 mcg/mL	Methadone	25 ng/mL
Benzodiazepines	100 ng/mL	Opiates	20 ng/mL
Cannabinoids	10 ng/mL	Phencyclidine	10 ng/mL
Cocaine / Metabolites	20 ng/mL	Propoxyphene	50 ng/mL

-Analysis by Gas Chromatography/Mass Spectrometry (GC/MS) for: The following is a general list of compound classes included in the Gas Chromatographic screen. The detection of any particular compound is concentration-dependent. Please note that not all known compounds included in each specified class or heading are included. Some specific compounds outside these classes are also included. For a detailed list of all compounds and reporting limits included in this screen, please contact NMS Labs.

Amphetamines, Analgesics (opioid and non-opioid), Anesthetics, Anticholinergic Agents, Anticonvulsant Agents, Antidepressants, Antiemetic Agents, Antihistamines, Antiparkinsonian Agents, Antipsychotic Agents, Anxiolytics (Benzodiazepine and others), Cardiovascular Agents (non-digitalis), Hallucinogens, Hypnosedatives (Barbiturates, Non-Benzodiazepine Hypnotics and others), Muscle Relaxants, Non-Steroidal Anti-Inflammatory Agents (excluding Salicylate) and Stimulants (Amphetamine-like and others).

-Analysis by Headspace Gas Chromatography (GC) for:

Compound	Rpt. Limit	Compound	Rpt. Limit
Acetone	1.0 mg/dL	Isopropanol	1.0 mg/dL
Ethanol	10 mg/dL	Methanol	5.0 mg/dL

Exhibit 2

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA warns about several safety issues with opioid pain medicines; requires label changes

Safety Announcement

[3-22-2016] The U.S. Food and Drug Administration (FDA) is warning about several safety issues with the entire class of opioid pain medicines. These safety risks are potentially harmful interactions with numerous other medications, problems with the adrenal glands, and decreased sex hormone levels. We are requiring changes to the labels of all opioid drugs to warn about these risks.

More specifically, the labels will warn about the following:

- Opioids can interact with antidepressants and migraine medicines to cause a serious central nervous system reaction called serotonin syndrome, in which high levels of the chemical serotonin build up in the brain and cause toxicity (see List of Serotonergic Medicines).
- Taking opioids may lead to a rare, but serious condition in which the adrenal glands do not produce adequate amounts of the hormone cortisol. Cortisol helps the body respond to stress.
- Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.

Opioids are a class of powerful narcotic pain medicines that are used to treat moderate to severe pain that may not respond well to other pain medicines (see List of Opioids). They can help manage pain when other treatments and medicines are not able to provide enough pain relief, but they also have serious risks including misuse and abuse, addiction, overdose, and death.

Recommendations and information for patients and health care professionals

Serotonin syndrome:

Patients taking an opioid along with a serotonergic medicine (see List of Serotonergic Medicines) should seek medical attention immediately if they develop symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea. Symptoms generally start within several hours to a few days of taking an opioid with another medicine that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase.

Health care professionals should discontinue opioid treatment and/or use of the other medicine if serotonin syndrome is suspected.

Cases of serotonin syndrome in the FDA Adverse Event Reporting System (FAERS) database were reported more frequently with the opioids fentanyl and methadone used at the recommended doses. Therefore, we are requiring a new statement in the *Warnings and Precautions* section to be added to these drug labels. Some opioids, including tramadol, tapentadol, and meperidine, already have warnings about serotonin syndrome. Cases were also reported with other opioids, so the labels of all these drugs will be updated to include information about serotonin syndrome in the *Drug Interactions* and *Adverse Reactions* sections.

Adrenal insufficiency:
Patients should seek medical attention if they experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure. **Health care professionals** should perform diagnostic testing if adrenal insufficiency is suspected. If diagnosed, treat with corticosteroids and wean the patient off of the opioid, if appropriate. If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.

We are requiring a new statement about adrenal insufficiency to be added to the *Warnings and Precautions* section of all opioid labels.

Decreased sex hormone levels:
Patients should inform their health care professionals if they experience symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.
Health care professionals should conduct laboratory evaluation in patients presenting with such signs or symptoms.

We reviewed published studies that assessed levels of sex hormones in patients taking opioids chronically;[1-21] however, all had limitations that make it difficult to determine whether the symptoms were caused by the opioids or other factors. The labels of some opioids already describe this possible risk, and we are now adding consistent information to the *Adverse Reactions* section of all opioid labels.

We urge patients and health care professionals to report side effects involving opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

List of Opioids

Generic Name	Found in Brand Name(s)
alfentanil	Alfenta
buprenorphine	Belbuca, Bunavail, Buprenex, Butrans, Suboxone, Zubsolv
butorphanol	No brand name currently marketed
codeine	Fioricet w/ codeine, Fiorinal w/ codeine, Tylenol w/ codeine
dihydrocodeine	Synalgos-DC
fentanyl	Abstral, Actiq, Duragesic, Fentora, Ionsys, Lazanda, Sublimaze, Subsys
hydrocodone	Anexsia, Hysingla ER, Lortab, Norco, Reprexain, Vicodin, Vicoprofen, Zohydro ER
hydromorphone	Dilaudid, Dilaudid-HP, Exalgo
meperidine	Demerol
methadone	Dolophine, Methadose
morphine	Astramorph PF, Duramorph PF, Embeda, Infumorph, Kadian, Morphabond, MS Contin
oxycodone	Oxaydo, Oxycet, Oxycontin, Percocet, Percodan, Roxicet, Roxicodone, Xartemis XR
oxymorphone	Opana, Opana ER
pentazocine	Talwin
remifentanil	Ultiva
sufentanil	Sufenta
tapentadol	Nucynta, Nucynta ER
tramadol	Conzip, Ultracet, Ultram, Ultram ER

List of Serotonergic Medicines

Generic Name	Found in Brand Name(s)
Selective Serotonin Reuptake Inhibitors (SSRIs)	
paroxetine	Paxil, Paxil CR, Pexeva, Brisdelle
fluvoxamine	Luvox, Luvox CR
fluoxetine	Prozac, Prozac Weekly, Sarafem, Selfemra, Symbyax
sertraline	Zoloft
citalopram	Celexa
escitalopram	Lexapro
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	
venlafaxine	Effexor XR
desvenlafaxine	Pristiq, Khedezla
duloxetine	Cymbalta
milnacipran	Savella
Tricyclic Antidepressants (TCAs)	
amitriptyline	No brand name currently marketed
desipramine	Norpramin
clomipramine	Anafranil
imipramine	Tofranil, Tofranil PM
nortriptyline	Pamelor, Aventyl
protriptyline	Vivactil
doxepin	Zonalon, Silenor
trimipramine	Surmontil
Monoamine Oxidase Inhibitors (MAOIs)	
isocarboxazid	Marplan
phenelzine	Nardil
selegiline	Emsam, Eldepryl, Zelapar
tranylcypromine	Parnate
Other Psychiatric Medicines	
amoxapine	No brand name currently marketed
maprotiline	No brand name currently marketed
nefazodone	No brand name currently marketed
trazodone	Oleptro
buspirone	No brand name currently marketed
vilazodone	Viibryd
mirtazapine	Remeron, Remeron Soltab
lithium	Lithobid
Migraine Medicines	
almotriptan	Axert
frovatriptan	Frova
naratriptan	Amerge

rizatriptan	Maxalt, Maxalt-MLT
sumatriptan	Imitrex, Imitrex Statdose, Alsuma, Sumavel Dosepro, Zecuity, Treximet
zolmitriptan	Zomig, Zomig-ZMT
Antiemetics	
ondansetron	Zofran, Zofran ODT, Zuplenz
granisetron	Kytril, Sancuso
dolasetron	Anzemet
palonosetron	Aloxi
Other Serotonergic Medicines	
dextromethorphan	Bromfed-DM, Delsym, Mucinex DM, Nuedexta
linezolid	Zyvox
cyclobenzaprine	Amrix
methylene blue	
St. John's wort	
tryptophan	

Facts about Opioids

- Opioids are powerful prescription medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief (see List of Opioid Medicines). However, opioids also carry serious risks, including of misuse and abuse, addiction, overdose, and death.
- Prescription opioids are divided into two main categories – immediate-release (IR) products, usually intended for use every 4 to 6 hours; and extended release/long acting (ER/LA) products, intended to be taken once or twice a day, depending on the individual product and patient.
- Certain opioids, such as methadone and buprenorphine, can also be prescribed as a form of treatment for opioid addiction.
- Opioids are available in many different formulations, including tablets, capsules, lozenges, sublingual tablets, transdermal patches, nasal sprays, and injections.
- Common side effects of opioids include drowsiness, dizziness, nausea, vomiting, constipation, physical dependence, and slowed or difficult breathing.
- The risk of opioid addiction, abuse or misuse is increased in patients with a personal or family history of substance abuse, or mental illness.
- It is important to lock up opioids and to dispose of them properly to keep them from falling into the wrong hands.

Additional Information for Patients

- FDA is warning about several safety issues with the class of powerful narcotic opioid pain medicines:

- Opioids can interact with certain medicines that increase the effects of serotonin, which is a chemical in the brain. The interacting medicines include antidepressants and migraine medicines, and the interaction causes a serious central nervous system reaction called serotonin syndrome (see List of Serotonergic Medicines).
- Taking opioids may lead to a rare, but serious condition called adrenal insufficiency in which the adrenal glands do not produce adequate amounts of the steroid hormone, cortisol, particularly during stressful conditions.
- Long-term use of opioids may be associated with decreased sex hormone levels.

- Inform your health care professional about all the drugs you are taking, including prescription and over-the-counter medicines. It is helpful to keep a list of all your current medicines in your wallet or another location where it can be easily retrieved. You can fill out and print a copy of My Medicine Record.
- If you are taking an opioid pain reliever and don't know if you are also receiving serotonergic medicines or other medicines that interact with opioids, contact your health care professional.
- Opioids are powerful narcotic pain medicines that can help manage pain when other treatments and medicines are not able to provide enough pain relief. However, even when used properly, opioids also carry serious risks, and they can be misused and abused, causing addiction, overdose, and death.
- Seek medical attention immediately if you develop any symptoms of serotonin syndrome such as:
  - Agitation
  - Hallucinations
  - Rapid heart rate
  - Fever
  - Excessive sweating
  - Shivering or shaking
  - Muscle twitching or stiffness
  - Trouble with coordination
  - Nausea, vomiting, or diarrhea
- Also seek medical attention if you experience symptoms of adrenal insufficiency such as:
  - Nausea or vomiting
  - Loss of appetite
  - Fatigue
  - Weakness
  - Dizziness
  - Low blood pressure.
- Inform your health care professional if you experience signs or symptoms of decreased sex hormone levels such as low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

- Talk to your health care professional if you have any questions or concerns about opioids or other medicines you are taking.
- Read the patient information leaflet or Medication Guide that comes with your filled prescription(s).
- Report side effects from opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with the class of opioid pain medicines. These include serotonin syndrome, adrenal insufficiency, and androgen deficiency.

Serotonin syndrome

- Serotonin syndrome can occur during concomitant use of opioids with serotonergic drugs. This may occur within the recommended dosage range.
- If concomitant use of an opioid with a serotonergic drug is warranted, carefully observe the patient, particularly during treatment initiation and dose increases.
- Symptoms of serotonin syndrome may include mental status changes such as agitation, hallucinations, or coma; autonomic instability such as tachycardia, labile blood pressure, or hyperthermia; and neurologic abnormalities such as hyperreflexia, incoordination, or rigidity.
- The onset of symptoms generally occurs within several hours to a few days of concomitant use but may occur later, particularly after dose increases.
- Discontinue opioid treatment and/or use of the concomitant serotonergic drug if serotonin syndrome is suspected.
- Counsel patients about the symptoms of serotonin syndrome and advise them to seek medical attention immediately if symptoms develop.
- Instruct patients to inform their health care professionals if they are taking or plan to take serotonergic drugs.

Adrenal insufficiency

- Cases of adrenal insufficiency have been reported with opioid use.
- Presentation of adrenal insufficiency may include nonspecific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure.
- If adrenal insufficiency is suspected, confirm with diagnostic testing as soon as possible. The patient should be treated with physiologic replacement doses of corticosteroids and weaned off of the opioid to allow adrenal function to recover.
- If the opioid can be discontinued, follow-up assessment of adrenal function should be performed to determine if treatment with corticosteroids can be discontinued.
- Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency.
- The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Androgen deficiency

- Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility.
- The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled in studies conducted to date.
- Patients presenting with symptoms or signs of androgen deficiency should undergo laboratory evaluation.

General information

- Encourage patients to read the information leaflets or Medication Guides that come with their filled prescription(s).
- Report adverse events involving opioids or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA investigated several safety issues associated with the class of opioid pain medicines:

- Serotonin syndrome
- Adrenal insufficiency
- Androgen deficiency

Serotonin syndrome

A search of the FDA Adverse Event Reporting System (FAERS) database for the period January 1, 1969, to June 12, 2013, identified 43 cases of serotonin syndrome in which opioids were used concomitantly with other serotonergic drugs. The review excluded meperidine, tramadol, and tapentadol, which were already labeled for the risk of serotonin syndrome at the time of the review. The most commonly reported opioids associated with serotonin syndrome were fentanyl (n=28), oxycodone (n=7), and methadone (n=5). Other reported opioids included hydromorphone, morphine, alfentanil/remifentanil/sufentanil, hydrocodone, naltrexone, and pentazocine. Although there were no reports of serotonin syndrome with an opioid used alone, five cases reported that serotonin syndrome occurred with the use of two or more opioids concurrently. All of these five cases reported use of fentanyl along with at least one other opioid [oxycodone (n=4), morphine (n=1), hydromorphone (n=1), and hydrocodone (n=1)].

Adrenal insufficiency

A search of FAERS for the period January 1, 1969, to February 5, 2014, identified 37 cases of adrenal insufficiency reported with the use of opioids. Twenty-seven cases reported opioid monotherapy, and 10 reported use of more than one opioid at the same time. The most commonly reported opioids associated with adrenal insufficiency were fentanyl (n=10) and oxycodone (n=10), followed by buprenorphine or

buprenorphine/naloxone (n=7), hydromorphone (n=6), and tramadol (n=4). When reported, the time to onset of adrenal insufficiency after the start of opioid therapy ranged from within 1 day to more than 1 year; however, many of the cases reported adrenal insufficiency after at least 1 month of use. Many of the patients were hospitalized. Of the 37 cases, 21 described that the patients received corticosteroid treatment. Sixteen cases reported discontinuing or reducing the dose of the opioid. Of the 16, nine of these patients improved, three had ongoing symptoms, and four did not report an outcome. Some patients experienced a relief in symptoms when they were switched from one opioid to another.

Androgen deficiency

We reviewed the medical literature to evaluate the association between opioids and androgen deficiency. [1-21] A range of studies in a variety of settings demonstrated decreased gonadal hormones in men and women taking long-term opioids. However, most of the studies were descriptive prevalence studies that did not include baseline values for the hormone levels, and there was a lack of comparability between the opioid-treated groups and control groups regarding medical, physical, lifestyle, and psychological factors that may influence gonadal hormone levels. Due to limitations of the studies, it is unclear whether the low gonadal hormone levels and associated symptoms and signs in men and women could be attributed to long-term opioid use or to other factors such as the patient's underlying medical condition warranting opioid treatment; physical, mental, or life stressors; weight changes; or concomitant medication or supplement use.

References

1. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009; 360:606-14.

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